TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

ORIGINAL ARTICLE

Multicentric Glioblastoma: A Retrospective Analysis of Demographic, Clinical, Molecular and Prognostic Characteristics

Semanur DABAK GÖNÜLAL,[1] Müge AKMANSU,[1] İsmail Kaan SERT,[1] Hüseyin BORA,[1] Gökhan KURT[2]

[1]Department of Radiation Oncology, Gazi University Hospital, Ankara-*Türkiye*
[2]Department of Neurosurgery, Gazi University Hospital, Ankara-*Türkiye*

OBJECTIVE

The objective of the study was to compare the demographic, clinical, molecular and prognostic characteristics and survival outcomes of patients with multicentric glioblastoma (GBM) with those of patients with unifocal GBM.

METHODS

Patients with GBM referred to a single radiation oncology department between September 2015 and September 2022 were retrospectively reviewed. All cases were reclassified according to the 2021 World Health Organization Classification of Tumors of the Central Nervous System, and isocitrate dehydrogenase-mutant tumors were excluded. The final cohort comprised 76 patients with unifocal and 20 with multicentric GBM. Survival was analysed with the Kaplan–Meier method and Cox regression.

RESULTS

Median progression-free survival was 6 months in the multicentric group and 9 months in the unifocal group (p=0.031); median overall survival was 8 and 13 months, respectively (p=0.021). Poor performance status (Eastern Cooperative Oncology Group [ECOG] >2: 50% vs. 2.6%), bihemispheric involvement (60% vs. 2.6%) and a higher Ki-67 index were significantly more frequent in multicentric GBM. In the unifocal cohort, ECOG performance status was an independent predictor of progression and, together with age, of mortality; gross total and subtotal resection were associated with better outcomes than biopsy. No independent prognostic factor was identified in the multicentric cohort. The proportion of multicentric cases increased numerically after 2020, coinciding with the COVID-19 pandemic.

CONCLUSION

Multicentric GBM is associated with poorer performance status, higher proliferative activity, more frequent bihemispheric involvement and shorter survival than unifocal GBM. Whether the post-2020 increase in multicentric presentations is related to COVID-19 should be investigated in larger prospective cohorts.

Keywords: Glioblastoma; multicentric glioblastoma; COVID-19.
Copyright © 2026, Turkish Society for Radiation Oncology

This study was presented as an oral presentation at the 13th Multidisciplinary Neuro-oncology Symposium, Istanbul, Türkiye, 18–19 November 2022.

Received: October 12, 2026
Accepted: October 21, 2026
Online: November 25, 2026

Accessible online at:
www.onkder.org

Dr. Semanur DABAK GÖNÜLAL
Gazi Üniversitesi Hastanesi,
Radyasyon Onkolojisi Kliniği,
Ankara-Türkiye
E-mail: sdabak61@gmail.com

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

INTRODUCTION

Glioblastoma (GBM) is the most common and most aggressive primary malignant brain tumor in adults. Defined in the 2021 World Health Organization (WHO) Classification of Tumors of the central nervous system (CNS) as an isocitrate dehydrogenase (IDH)-wildtype diffuse astrocytic glioma of CNS WHO grade 4, GBM accounts for approximately half of all primary malignant brain tumors.[1] The standard first-line treatment consists of maximal safe resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide; nevertheless, median overall survival (OS) remains around 15 months.[2]

Within the clinical spectrum of GBM, tumors presenting with more than one lesion pose a particular management challenge. Multifocal GBM refers to multiple lesions connected by a recognizable route of spread, such as white-matter tracts or cerebrospinal fluid and leptomeningeal dissemination, whereas multicentric GBM refers to anatomically separate lesions that cannot be explained by any known pathway of spread.[3] The reported incidence of multifocal/multicentric GBM ranges from 2% to 35%, and true multicentric tumors are estimated to account for approximately 10% of all cases.[4,5] Both subgroups have been associated with a poorer prognosis, lower rates of gross total resection and a higher risk of recurrence than unifocal GBM.[6,7]

In our clinic, an apparent increase in the number of multicentric GBM cases since 2020 drew attention due to its temporal overlap with the COVID-19 pandemic. The aim of this study was to compare the demographic, clinical, molecular and survival characteristics of patients with multicentric and unifocal GBM and to explore this possible association.

MATERIALS AND METHODS

Study Design and Patients

This single-center retrospective study screened 116 patients with GBM who were referred to the radiation oncology department of a tertiary university hospital between September 2015 and September 2022. All cases were re-evaluated according to the 2021 WHO Classification of Tumors of the CNS, and 20 patients with IDH-mutant tumors, which are no longer classified as GBM, were excluded (n=20). The final study population consisted of 96 patients: 76 with unifocal and 20 with multicentric GBM.

Multicentric disease was defined on contrast-enhanced T1-weighted and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) as two or more anatomically separate lesions without a detectable connection or known route of spread.[3] Demographic data, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor location and hemispheric involvement, extent of resection (biopsy, subtotal resection [STR] or gross total resection [GTR]), p53 status, Ki-67 proliferation index, RT dose and survival status were retrieved from medical records. RT was delivered with intensity-modulated RT, volumetric-modulated arc therapy or three-dimensional conformal RT to a total dose of 60 Gy; patients with poor performance status received a hypofractionated regimen of 40 Gy in 15 fractions. All patients received concomitant and adjuvant temozolomide. Follow-up MRI was performed 1 month after the completion of RT and every 3 months thereafter. For patients diagnosed after the onset of the pandemic, history of COVID-19 infection and vaccination was recorded where available.

Ethics

The study was approved by the Şişli Memorial Hospital Ethics Committee (Decision no: 006, Date: December 12, 2023) and was conducted in accordance with the Declaration of Helsinki.

Owing to the retrospective design, informed consent was not obtained from patients. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Statistical Analysis

Analyses were performed with IBM Statistical Package for the Social Sciences Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. As continuous variables were not normally distributed, they were compared with the Mann–Whitney U test and are presented as median (minimum–maximum) together with mean±standard deviation. Categorical variables were compared with Pearson's Chi-square test, the Chi-square test with Yates' continuity correction or Fisher's exact test, as appropriate, and are presented as number (percentage). Progression-free survival (PFS) was defined as the time from diagnosis to progression, death or last follow-up, and OS as the time from diagnosis to death or last follow-up, both in months. Survival was estimated with the Kaplan–Meier method and compared with the log-rank test. Factors associated with PFS and OS were analysed separately within each cohort using univariate and multivariate Cox proportional hazards regression, and results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Variables that made the multivariate

Table 1 Comparison of categorical variables between patients with multicentric and unifocal GBM

	Multicentric GBM (n=20)	Unifocal GBM (n=76)	Test statistic	p
Age group (years)				
<60	9 (45.0)	40 (52.6)	0.127	0.722[b]
≥60	11 (55.0)	36 (47.4)		
Sex				
Female	10 (50.0)	29 (38.2)	0.495	0.482[b]
Male	10 (50.0)	47 (61.8)		
ECOG PS				
0–2	10 (50.0)	74 (97.4)	–	**<0.001**[c]
>2	10 (50.0)	2 (2.6)		
Extent of resection				
Biopsy	1 (5.0)	5 (6.6)	1.726	0.422[a]
GTR	1 (5.0)	12 (15.8)		
STR	18 (90.0)	59 (77.6)		
p53 mutation				
Negative	2 (18.2)	20 (29.0)	–	0.718[c]
Positive	9 (81.8)	49 (71.0)		
RT dose				
<60 Gy	6 (30.0)	15 (19.7)	–	0.366[c]
≥60 Gy	14 (70.0)	61 (80.3)		
Ki-67 index				
≤20%	0 (0)	31 (44.9)	–	**0.005**[c]
>20%	10 (100)	38 (55.1)		
Hemispheric involvement				
Bihemispheric	12 (60.0)	2 (2.6)	–	**<0.001**[c]
Unihemispheric	8 (40.0)	74 (97.4)		
Tumor location				
Infratentorial	0 (0)	1 (1.3)	4.174	0.124[a]
Supratentorial	18 (90.0)	74 (97.4)		
Supratentorial and infratentorial	2 (10.0)	1 (1.3)		
Survival status				
Deceased	14 (70.0)	58 (76.3)	0.084	0.772[b]
Alive	6 (30.0)	18 (23.7)		

Data are presented as n (%); percentages are calculated among patients with available data. [a]: Pearson's Chi-square test; [b]: chi-square test with Yates' continuity correction; [c]: Fisher's exact test. GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GTR: Gross total resection; STR: Subtotal resection; RT: Radiotherapy.

models unstable were not included in them, and tumor location was not entered into the Cox models due to the small number of observations in some categories. A two-sided p<0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Multicentric disease accounted for 20.8% (20/96) of the study population. In the multicentric group, the female-to-male ratio was 1:1, and the median age was 62.5 (range, 27–74) years. ECOG PS 0–2 was observed in 50% of patients with multicentric GBM and in 97.4% of those with unifocal GBM (p<0.001). Bihemispheric involvement was present in 60% of the multicentric group and in 2.6% of the unifocal group (p<0.001). A Ki-67 index >20% was found in all evaluable multicentric tumors (10/10) compared with 55.1% of unifocal tumors (p=0.005). Age group, sex, extent of resection, p53 status, RT dose, tumor location and survival status did not differ significantly between the groups (Table 1).

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

Table 2 Comparison of continuous variables between patients with multicentric and unifocal GBM

	Multicentric GBM (n=20)		Unifocal GBM (n=76)		Test statistic	p[a]
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)		
Age (years)	57.25±13.47	62.5 (27–74)	56.55±12.90	58 (29–77)	712	0.655
Time to progression (months)	6.18±5.42	5 (1–26)	10.16±8.35	7.5 (0.3–39)	740	**0.023**
Follow-up (months)	9.15±10.06	6 (1–48)	16.37±11.52	12 (0.3–51)	1154.5	**<0.001**
ECOG PS	2.35±0.75	2.5 (1–3)	1.12±0.80	1 (0–3)	229	**<0.001**
RT dose (Gy)	55.33±8.58	60 (34–60)	57.30±6.21	60 (39–60)	841	0.312
Ki-67 index (%)	58±15	60 (35–85)	33±21	30 (1–90)	114	**0.001**

[a]: Mann–Whitney U test. GBM: Glioblastoma; SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy.

Table 3 Kaplan–Meier estimates of progression-free survival according to patient group

Group	Mean (95% CI)	Median (95% CI)	p[a]
Multicentric GBM	7.95 (3.72–12.19)	6 (4.76–7.24)	**0.031**
Unifocal GBM	14.58 (11.45–17.72)	9 (7.15–10.85)	
Total	13.52 (10.76–16.27)	8 (6.66–9.34)	

Survival times are given in months. [a]: Log-rank test. CI: Confidence interval; GBM: Glioblastoma.

Table 4 Kaplan–Meier estimates of overall survival according to patient group

Group	Mean (95% CI)	Median (95% CI)	p[a]
Multicentric GBM	13.99 (4.87–23.12)	8 (4.94–11.06)	**0.021**
Unifocal GBM	19.53 (15.88–23.18)	13 (10.96–15.04)	
Total	18.33 (15.03–21.64)	12 (10.36–13.65)	

Survival times are given in months. aLog-rank test. CI: Confidence interval; GBM: Glioblastoma.

In the comparison of continuous variables, median time to progression was 5 months in the multicentric group and 7.5 months in the unifocal group (p=0.023), and median follow-up was 6 and 12 months, respectively (p<0.001). The median Ki-67 index was 60% in the multicentric group and 30% in the unifocal group (p=0.001) (Table 2).

Survival

Median PFS was 6 months (95% CI: 4.76–7.24) in the multicentric group and 9 months (95% CI: 7.15–10.85) in the unifocal group (p=0.031) (Table 3 and Fig. 1). Median OS was 8 months (95% CI: 4.94–11.06) and 13 months (95% CI: 10.96–15.04), respectively (p=0.021) (Table 4 and Fig. 2).

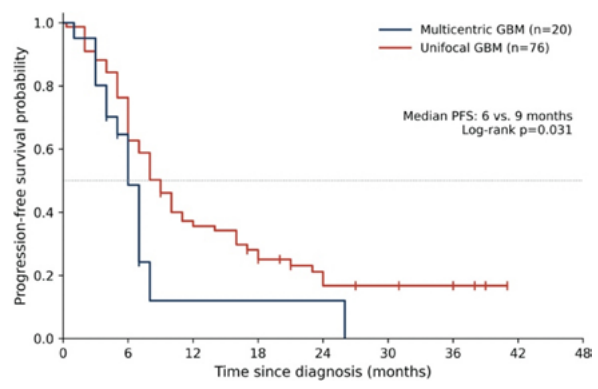


Fig. 1. Kaplan–Meier curves of progression-free survival in patients with multicentric and unifocal glioblastoma. Vertical tick marks indicate censored observations. The dotted horizontal line indicates a survival probability of 0.5.

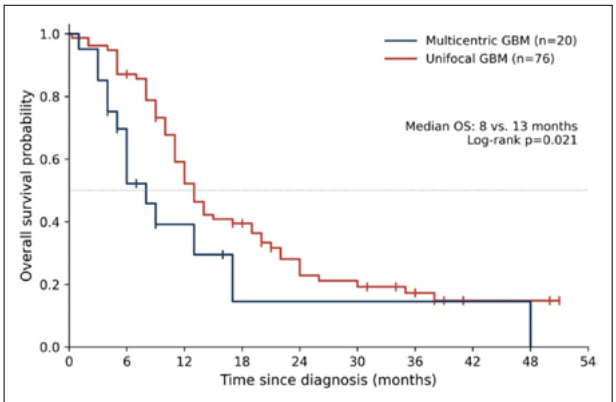


Fig. 2. Kaplan–Meier curves of overall survival in patients with multicentric and unifocal glioblastoma. Vertical tick marks indicate censored observations. The dotted horizontal line indicates a survival probability of 0.5.

Table 5 Cox regression analysis of factors associated with progression-free survival within each patient group

Cohort	Variable	Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Multicentric GBM	Age	1.035 (0.985–1.087)	0.177	0.937 (0.753–1.167)	0.562
	Sex	2.323 (0.689–7.836)	0.174	11.124 (0.639–193.741)	0.098
	ECOG PS	2.027 (0.849–4.837)	0.112	1.692 (0.072–39.739)	0.744
	Ki-67 index	6.192 (0.076–507.376)	0.417	0.001 (<0.001–>1000)	0.463
	p53 mutation	2.036 (0.229–18.066)	0.523	–	–
	RT dose (Gy)	0.963 (0.908–1.021)	0.210	1.052 (0.897–1.235)	0.532
	Extent of resection (ref: biopsy)				
	GTR	0.751 (<0.001–>1000)	0.972	–	–
	STR	24.613 (<0.001–>1000)	0.661	–	–
	Hemispheric involvement	0.658 (0.209–2.071)	0.474	0.004 (<0.001–6.965)	0.145
Unifocal GBM	Age	1.021 (0.997–1.046)	0.084	1.021 (0.992–1.050)	0.158
	Sex	1.317 (0.765–2.266)	0.321	0.958 (0.525–1.748)	0.890
	ECOG PS	3.323 (2.207–5.005)	**<0.001**	3.448 (2.118–5.613)	**<0.001**
	Ki-67 index	1.083 (0.292–4.013)	0.905	0.621 (0.156–2.479)	0.500
	p53 mutation	0.958 (0.517–1.776)	0.893	–	–
	RT dose (Gy)	0.989 (0.944–1.037)	0.656	0.992 (0.940–1.046)	0.761
	Extent of resection (ref: biopsy)				
	GTR	0.013 (0.003–0.058)	**<0.001**	–	–
	STR	0.127 (0.045–0.361)	**<0.001**	–	–
	Hemispheric involvement	0.321 (0.076–1.348)	0.120	0.651 (0.145–2.932)	0.577

–: Not included in the multivariate model. Ki-67 index was entered as a continuous variable (0–1 scale). Extent of resection was analysed with biopsy as the reference category. Confidence limits below 0.001 or above 1000 are shown as <0.001 or >1000 (unstable estimates owing to the small number of events). HR: Hazard ratio; CI: Confidence interval; GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy; GTR: Gross total resection; STR: Subtotal resection.

Prognostic Factors

In the Cox analysis for PFS (Table 5), ECOG PS was an independent prognostic factor in the unifocal cohort (multivariate HR: 3.448, 95% CI: 2.118–5.613, p<0.001). In univariate analysis, both GTR (HR: 0.013, 95% CI: 0.003–0.058, p<0.001) and STR (HR: 0.127, 95% CI: 0.045–0.361, p<0.001) were associated with a significantly lower risk of progression than biopsy. In the analysis for OS (Table 6), age (HR: 1.037, 95% CI: 1.006–1.070, p=0.019) and ECOG PS (HR: 6.184, 95% CI: 3.568–10.719, p<0.001) were independent predictors of mortality in the unifocal cohort. No independent prognostic factor was identified in the multicentric cohort in either analysis (all p>0.05).

Distribution by Year of Diagnosis

Of the 20 multicentric cases, 10 were diagnosed between 2015 and 2019 and 10 between 2020 and 2022. Relative to all screened patients, the proportion of multicentric cases increased from 13.3% (10/75) in 2015–2019 to 24.4% (10/41) in 2020–2022, with the highest annual number (n=6) recorded in 2022; however, this difference was not statistically significant (Fisher's exact test, p=0.197) (Fig. 3). Among patients diagnosed after the onset of the pandemic with available data, four patients had a history of COVID-19 vaccination and four other patients had a history of COVID-19 infection.

DISCUSSION

The management of GBM requires an effective multidisciplinary approach involving neurosurgery, radiation oncology and medical oncology. The reported incidence of multifocal/multicentric GBM ranges from 2% to 35%.[4,5,8] This wide range largely reflects differences in definitions and imaging techniques. The classical criteria of Batzdorf and Malamud defined multicentric gliomas as widely separated lesions, located in different lobes or hemispheres, without any macroscopic or microscopic connection.[9] With modern MRI, and especially FLAIR sequences, connections can be seen between lesions that once appeared separate, so some apparently multicentric tumors are reclassi-

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

Table 6 Cox regression analysis of factors associated with overall survival within each patient group

Cohort	Variable	Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Multicentric GBM	Age	1.025 (0.977–1.075)	0.321	0.920 (0.759–1.114)	0.393
	Sex	2.239 (0.661–7.585)	0.195	15.564 (0.722–335.626)	0.080
	ECOG PS	2.126 (0.905–4.996)	0.084	1.944 (0.189–19.983)	0.576
	Ki-67 index	6.778 (0.065–705.004)	0.419	0.001 (<0.001–>1000)	0.435
	p53 mutation	1.676 (0.184–15.243)	0.646	–	–
	RT dose (Gy)	0.973 (0.920–1.029)	0.337	1.024 (0.889–1.180)	0.743
	Extent of resection (ref: biopsy)				
	GTR	0.737 (<0.001–>1000)	0.972	–	–
	STR	24.478 (<0.001–>1000)	0.688	–	–
	Hemispheric involvement	0.852 (0.277–2.618)	0.780	0.004 (<0.001–9.579)	0.166
Unifocal GBM	Age	1.026 (1.001–1.052)	0.045	1.037 (1.006–1.070)	0.019
	Sex	1.389 (0.806–2.394)	0.236	1.001 (0.547–1.834)	0.997
	ECOG PS	5.449 (3.441–8.628)	**<0.001**	6.184 (3.568–10.719)	**<0.001**
	Ki-67 index	1.442 (0.373–5.581)	0.596	1.862 (0.458–7.566)	0.385
	p53 mutation	0.821 (0.442–1.524)	0.532	–	–
	RT dose (Gy)	0.986 (0.941–1.033)	0.547	0.984 (0.933–1.038)	0.553
	Extent of resection (ref: biopsy)				
	GTR	0.002 (<0.001–0.016)	**<0.001**	–	–
	STR	0.042 (0.012–0.149)	**<0.001**	–	–
	Hemispheric involvement	0.604 (0.146–2.501)	0.487	0.880 (0.202–3.830)	0.865

–: Not included in the multivariate model. Ki-67 index was entered as a continuous variable (0–1 scale). Extent of resection was analysed with biopsy as the reference category. Confidence limits below 0.001 or above 1000 are shown as <0.001 or >1000 (unstable estimates owing to the small number of events). HR: Hazard ratio; CI: Confidence interval; GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy; GTR: Gross total resection; STR: Subtotal resection.

fied as multifocal.[3] In a meta-analysis by Di Carlo et al.,[10] multiple lesions were present in 19% of high-grade gliomas, with multicentric and multifocal tumors accounting for 6% and 11%, respectively. Thomas et al.[11] found multiple lesions at diagnosis in 35% of patients with GBM and suggested that improved imaging partly explains the higher rates reported in recent series. In our series, the proportion of multicentric GBM was 20.8%, which is higher than in many previously reported series. We attribute this relatively high rate to the technical capacity of our center and the high volume of referrals from other centres; a referral-related selection bias therefore cannot be excluded.

Age and sex distributions did not differ significantly between the groups. The median age of our multicentric group (62.5 years) was close to the median age at GBM diagnosis reported in population-based registry data (66 years).[12] Although GBM is about 1.6 times more common in men than in women,[12] the sex ratio in our multicentric group was 1:1; given the small number of patients, this finding should not be over-interpreted.

Our survival findings are largely consistent with the literature. Patil et al.[6] reported significantly shorter survival in patients with multifocal GBM than in those with unifocal disease, and Lasocki et al.[3] emphasised

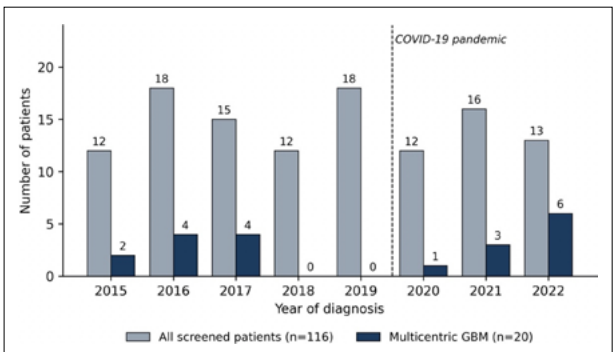


Fig. 3. Annual distribution of all screened patients and of patients with multicentric glioblastoma by year of diagnosis. The dashed line marks the onset of the COVID-19 pandemic. The study period covered September 2015 to September 2022; therefore, 2015 and 2022 represent partial years.

the role of FLAIR imaging in the characterization and prognostic classification of multifocal and multicentric GBM. In the meta-analysis by Di Carlo et al.,[10] the presence of multiple lesions was associated with a 1.71-fold higher risk of death. In contrast, Paulsson et al.[13] found no appreciable difference in survival, patterns of failure, or genomic signatures between single-focus and multiple-lesion GBM, suggesting that the prognostic impact of lesion multiplicity may vary between series. Thomas et al.[11] offered a possible explanation for these conflicting results: patients with multiple lesions had shorter median OS than those with a single lesion (10 vs. 18 months), but this difference was no longer significant after adjustment for age, Karnofsky performance status, and extent of resection. This observation is directly relevant to our findings, because 50% of our patients with multicentric GBM had an ECOG PS >2, compared with only 2.6% of those with unifocal GBM. The shorter survival of the multicentric group may therefore reflect, at least in part, its poorer clinical condition at presentation rather than lesion multiplicity alone. The small size of the multicentric cohort did not allow us to test this hypothesis in a combined multivariate model.

The independent prognostic value of ECOG PS and age in our unifocal cohort is in line with established prognostic models. In the Radiation Therapy Oncology Group recursive partitioning analysis and in later series, age and performance status consistently emerged as the strongest determinants of survival in GBM,[14,15] and the systematic review by Li et al.[16] also supports the prognostic importance of performance status. In our unifocal cohort, both GTR and STR were associated with a lower risk of progression than biopsy, and the favorable association of GTR with survival (univariate HR for OS: 0.002, $p<0.001$) is in line with the findings of Haque et al.[7] Larger series and meta-analyses support this observation: Lacroix et al.[17] reported a significant survival advantage when at least 98% of the tumor volume was removed, and the meta-analysis by Brown et al.[18] showed that GTR improves both OS and PFS compared with STR.

Bihemispheric involvement, present in 60% of the multicentric group, makes GTR technically difficult and often limits surgery to biopsy. Although the extent of resection did not differ significantly between the groups in our series, the literature suggests that surgery should not be abandoned in multicentric disease when it can be performed safely. Hassaneen et al.[19] showed that resection of all lesions through multiple craniotomies in multifocal and multicentric GBM provided survival comparable to that of matched patients with a single lesion, without an increase in complications. Similarly, in the meta-analysis by Di Carlo et al.,[10] surgical resection was an independent predictor of better outcome in multicentric tumors, whereas biopsy alone was associated with a markedly higher risk of death (HR: 7.61). In butterfly GBM, another form of bihemispheric disease, Dziurzynski et al.[20] reported a median survival of 265 days after surgical decompression and 48 days after biopsy, although this difference did not reach statistical significance. The absence of an independent prognostic factor in our multicentric cohort is most likely explained by the small number of patients and events rather than by a true lack of effect.

Showalter et al.[21] reported that local recurrence predominated in multifocal GBM, whereas Syed et al.[22] showed that distant intracranial recurrence was also a substantial problem. These patterns support covering all visible lesions within the RT target volumes, while remaining alert to distant progression during follow-up. In our series, patients with poor performance status received hypofractionated RT (40 Gy in 15 fractions). This approach is supported by randomised data showing that an abbreviated course provides survival similar to that of the standard 60 Gy regimen in older patients,[23] and that adding temozolomide to short-course RT prolongs survival in elderly patients.[24] Because half of our patients with multicentric GBM had an ECOG PS >2, short-course regimens are a practical option that reduces treatment burden in this subgroup.

The higher Ki-67 proliferation index in the multicentric group (median 60% vs. 30%) is consistent with the report by Liu et al.,[25] which pointed to a distinct molecular profile in multifocal and multicentric GBM. Dono et al.[26] also examined the molecular characteristics and clinical features of multifocal GBM. The origin of multiple lesions is still debated. Abou-El-Ardat et al.[27] showed that separate foci in the same patient share early genetic events, such as loss of chromosome 10 and TERT promoter mutations, supporting a monoclonal origin followed by parallel clonal evolution. Lim et al.[28] reported that GBMs in contact with the subventricular zone, a neural stem cell niche, were more often multifocal. A highly proliferative and invasive phenotype may therefore facilitate the development of distant lesions. However, the prognostic value of Ki-67 in GBM remains controversial: Tini et al.[29] found that a Ki-67 index below 15% independently predicted longer survival in IDH-wildtype GBM, whereas Alkhaibary et al.[30] found no significant association with survival. In addition, Ki-67 data were available for only half of our multicentric patients, so this finding should be confirmed in larger series.

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

Relationship with the COVID-19 Pandemic

The increase in multicentric GBM observed after 2020 warrants investigation of possible biological mechanisms. Using a Mendelian randomization approach, Dong et al.[31] showed that COVID-19 hospitalisation increased the risk of developing GBM. The expression of angiotensin-converting enzyme 2 (ACE2) in human neurons supports the neuroinvasive potential of SARS-CoV-2,[32] and Jiang et al.[33] reported that the coronavirus receptors ANPEP and ENPEP are significantly overexpressed in GBM tissue and can form protein complexes with ACE2. In a retrospective case–control study from the MD Anderson Cancer Center, patients with GBM showed accelerated tumor progression after COVID-19 infection, and multifocal or leptomeningeal disease at progression was more frequent in infected patients than in controls.[34] Systemic inflammation is another possible link: In experimental models, respiratory viral infections, including SARS-CoV-2, reactivated dormant disseminated cancer cells through an interleukin-6-dependent mechanism, and in human cohorts SARS-CoV-2 infection was associated with higher cancer mortality and lung metastasis in patients with breast cancer.[35] Whether similar inflammatory signaling affects glial tumors remains unknown. On the other hand, delayed presentation during the pandemic, resulting in diagnosis at a more advanced stage, may be an indirect explanation for this increase.[36] It should also be stressed that the increase in our series did not reach statistical significance (p=0.197) and that infection and vaccination histories were available for only some patients; therefore, no conclusion regarding COVID-19 infection or vaccination can be drawn from these data. This observation should be regarded as hypothesis-generating; both possibilities deserve thorough investigation, and this study aims to draw attention to this question.

Limitations of the Study

The main limitations of this study are its retrospective design, the relatively small sample size – particularly in the multicentric group – and the inability to reach some patients during the pandemic. The small number of patients and events in the multicentric cohort limited the statistical power of the Cox models, as reflected by the wide CIs, and the multivariate results in this group should be interpreted with caution. Molecular data were incomplete for some patients, and O6-methylguanine-DNA methyltransferase promoter methylation status, the main predictor of benefit from temozolomide,[37] was not available. Nevertheless, to our knowledge, this is one of the few single-center series focusing specifically on multicentric GBM classified according to the 2021 WHO criteria.

CONCLUSION

Multicentric GBM is associated with a significantly worse prognosis than unifocal disease and is characterised by poor performance status, high proliferative activity, frequent bihemispheric involvement and limited options for complete resection. The increase in incidence that temporally coincided with the COVID-19 pandemic raises a new question that requires investigation of both direct biological and indirect clinical mechanisms. Large multicenter prospective studies are needed to clarify the prognostic determinants specific to this subgroup and to optimize treatment strategies.

Ethics Committee Approval: The study was approved by the Şişli Memorial Hospital Ethics Committee (no: 006, date: 12/12/2023).

Informed Consent: Informed consent was waived due to the retrospective design of the study.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Funding: This study received no financial support from any institution or organisation.

Use of AI for Writing Assistance: AI-assisted tools were used for language editing and readability improvement of the manuscript text. All scientific content, data analysis, interpretation, and conclusions are the sole responsibility of the authors.

Author Contributions: Concept – S.D.G., İ.K.S., H.B., G.K.; Design – S.D.G., M.A., İ.K.S., H.B., G.K.; Supervision – M.A.; Materials – G.K.; Data collection and/or processing – S.D.G., M.A., H.B.; Data analysis and/or interpretation – S.D.G., M.A., H.B.; Literature search – S.D.G.; Writing – S.D.G., H.B.; Critical review – M.A., İ.K.S., G.K.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, et al. Epidemiology of Glioblastoma Multiforme-Literature Review. Cancers (Basel) 2022;14:2412.
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.

3. Lasocki A, Gaillard F, Tacey M, Drummond K, Stuckey S. Multifocal and multicentric glioblastoma: Improved characterisation with FLAIR imaging and prognostic implications. J Clin Neurosci 2016;31:92–8.
4. Farhat M, Fuller GN, Wintermark M, Chung C, Kumar VA, Chen M. Multifocal and multicentric glioblastoma: Imaging signature, molecular characterization, patterns of spread, and treatment. Neuroradiol J 2023:19714009231193162.
5. Salvati M, Caroli E, Orlando ER, Frati A, Artizzu S, Ferrante L. Multicentric glioma: our experience in 25 patients and critical review of the literature. Neurosurg Rev 2003;26:275–9.
6. Patil CG, Yi A, Elramsisy A, Hu J, Mukherjee D, Irvin DK, et al. Prognosis of patients with multifocal glioblastoma: a case-control study. J Neurosurg 2012;117:705–11.
7. Haque W, Thong Y, Verma V, Rostomily R, Butler EB, Teh BS. Patterns of management and outcomes of unifocal versus multifocal glioblastoma. J Clin Neurosci 2020;74:155–9.
8. Baro V, Cerretti G, Todoverto M, Della Puppa A, Chioffi F, Volpin F, et al. Newly diagnosed multifocal GBM: A monocentric experience and literature review. Curr Oncol 2022;29:3472–88.
9. Batzdorf U, Malamud N. The problem of multicentric gliomas. J Neurosurg 1963;20:122–36.
10. Di Carlo DT, Cagnazzo F, Benedetto N, Morganti R, Perrini P. Multiple high-grade gliomas: Epidemiology, management, and outcome. A systematic review and meta-analysis. Neurosurg Rev 2019;42:263–75.
11. Thomas RP, Xu LW, Lober RM, Li G, Nagpal S. The incidence and significance of multiple lesions in glioblastoma. J Neurooncol 2013;112:91–7.
12. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 2023;25(Suppl 4):iv1–iv99.
13. Paulsson AK, Holmes JA, Peiffer AM, Miller LD, Liu W, Xu J, et al. Comparison of clinical outcomes and genomic characteristics of single focus and multifocal glioblastoma. J Neurooncol 2014;119:429–35.
14. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993;85:704–10.
15. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: Recursive partitioning analysis. Neuro Oncol 2004;6:227-35.
16. Li Y, Zhang ZX, Huang GH, Xiang Y, Yang L, Pei YC, et al. A systematic review of multifocal and multicentric glioblastoma. J Clin Neurosci 2021;83:71–6.
17. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. J Neurosurg 2001;95:190–8.
18. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblastoma: A systematic review and meta-analysis. JAMA Oncol 2016;2:1460–9.
19. Hassaneen W, Levine NB, Suki D, Salaskar AL, de Moura Lima A, McCutcheon IE, et al. Multiple craniotomies in the management of multifocal and multicentric glioblastoma. J Neurosurg 2011;114:576–84.
20. Dziurzynski K, Blas-Boria D, Suki D, Cahill DP, Prabhu SS, Puduvalli V, et al. Butterfly glioblastomas: a retrospective review and qualitative assessment of outcomes. J Neurooncol 2012;109:555–63.
21. Showalter TN, Andrel J, Andrews DW, Curran WJ Jr, Daskalakis C, Werner-Wasik M. Multifocal glioblastoma multiforme: Prognostic factors and patterns of progression. Int J Radiat Oncol Biol Phys 2007;69:820–4.
22. Syed M, Liermann J, Verma V, Bernhardt D, Bougatf N, Paul A, et al. Survival and recurrence patterns of multifocal glioblastoma after radiation therapy. Cancer Manag Res 2018;10:4229–35.
23. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 2004;22:1583–8.
24. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 2017;376:1027–37.
25. Liu Q, Liu Y, Li W, Wang X, Sawaya R, Lang FF, et al. Genetic, epigenetic, and molecular landscapes of multifocal and multicentric glioblastoma. Acta Neuropathol 2015;130:587–97.
26. Dono A, Wang E, Lopez-Rivera V, Ramesh AV, Tandon N, Ballester LY, et al. Molecular characteristics and clinical features of multifocal glioblastoma. J Neurooncol 2020;148:389–97.
27. Abou-El-Ardat K, Seifert M, Becker K, Eisenreich S, Lehmann M, Hackmann K, et al. Comprehensive molecular characterization of multifocal glioblastoma proves its monoclonal origin and reveals novel insights into clonal evolution and heterogeneity of glioblastomas. Neuro Oncol 2017;19:546–57.
28. Lim DA, Cha S, Mayo MC, Chen MH, Keles E, VandenBerg S, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9:424–9.
29. Tini P, Yavoroska M, Mazzei MA, Miracco C, Pirtoli L, Tomaciello M, et al. Low expression of Ki-67/MIB-1

Turk J Oncol 2026;41(4):349–358
doi: 10.5505/tjo.2026.11299

labeling index in IDH wild type glioblastoma predicts prolonged survival independently by MGMT methylation status. J Neurooncol 2023;163:339–44.
30. Alkhaibary A, Alassiri AH, AlSufiani F, Alharbi MA. Ki-67 labeling index in glioblastoma; does it really matter? Hematol Oncol Stem Cell Ther 2019;12:82–8.
31. Dong J, Wang S, Xie H, Mou Y, Zhu H, Peng Y, et al. COVID-19 hospitalization increases the risk of developing glioblastoma: A bidirectional Mendelian-randomization study. Front Oncol 2023;13:1185466.
32. Xu J, Lazartigues E. Expression of ACE2 in human neurons supports the neuro-invasive potential of COVID-19 virus. Cell Mol Neurobiol 2022;42:305–9.
33. Jiang Y, Zhao J, Li R, Liu Y, Zhou L, Wang C, et al. Comprehensive oncogenic features of coronavirus receptors in glioblastoma multiforme. Front Immunol 2022;13:840785.
34. Gregory TA, Knight SR, Aaroe AE, Highsmith KN, Janatpour ZC, O'Brien BJ, et al. Accelerated tumor progression after COVID-19 infection in patients with glioblastoma: A retrospective case-control study. Neurooncol Pract 2024;11:475–83.
35. Chia SB, Johnson BJ, Hu J, Valença-Pereira F, Chadeau-Hyam M, Guntoro F, et al. Respiratory viral infections awaken metastatic breast cancer cells in lungs. Nature 2025;645:496–506.
36. Tambuyzer T, Vanhauwaert D, Boterberg T, De Vleeschouwer S, Peacock HM, Bouchat J, et al. Impact of the COVID-19 pandemic on incidence and observed survival of malignant brain tumors in Belgium. Cancers (Basel) 2023;16:63.
37. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997–1003.